Short-course therapy for tuberculosis in infants and children

Infectious Diseases and Immunization Committee, Canadian Paediatric Society

Objective: To improve efficacy of and compliance with therapy for tuberculosis in children.
Options: Short-course (6-month) multi-drug therapy, either nonsupervised or directly supervised, versus long-course (more than 6-month) multi-drug therapy.
Outcomes: Success (more than 90% of cases cured without relapse or serious side effects), development of drug resistance and compliance with treatment.
Evidence: Review of published reports of efficacy trials of tuberculosis therapy in children, side effects and compliance studies; consensus of expert opinion.
Values: Values were assigned to the evidence by the Infectious Disease and Immunization Committee of the Canadian Paediatric Society through review of the data and consensus.
Benefits, harms and costs: Improved efficacy and compliance with short-course protocols should lower the rate of treatment failure among children in Canada and the cost of tuberculosis care.
Recommendations: A short-course (6-month) protocol of four drugs for the first 2 months and two drugs for the subsequent 4 months is recommended to treat pulmonary tuberculosis or extrapulmonary disease causing lymphadenopathy. Tuberculous meningitis, disease involving bones and joints and tuberculosis with HIV infection require longer courses of treatment. Asymptomatic tuberculosis should be treated with daily doses of isoniazid for 9 months. Intermittent directly observed therapy is recommended if compliance cannot be ensured. Routine liver function testing is not recommended for prepubescent children taking isoniazid, but monthly assessment for clinical symptoms and periodic liver function evaluation is advised in adolescent women, especially post partum.
Validation: This report was reviewed by the directors of the Canadian Paediatric Society, the Hepatitis and Special Pathogens Division of the Laboratory Centre for Disease Control and the Canadian Thoracic Society. The recommendations are similar to those of the American Academy of Pediatrics.
Sponsor: The recommendations were developed and endorsed by the Infectious Disease and Immunization Committee of the Canadian Paediatric Society.

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Objectif : Améliorer l'efficacité et le respect du traitement de la tuberculose chez les enfants.
Options : Pharmacothérapie multiple de courte durée (6 mois), sans surveillance ou sous surveillance directe, ou pharmacothérapie multiple de longue durée (plus de 6 mois).
Résultats : Réussite (plus de 90 % des cas guéris sans rechute ou effets secondaires graves), apparition de la pharmacorésistance et respect du traitement.
Preuve : Revue de rapports publiés sur des études d'efficacité de traitement de la tuberculose chez les enfants, effets secondaires et études d'observation; consensus d'experts.
Valeurs : Le Comité des maladies infectieuses et d'immunisation de la Société canadienne de pédiatrie a attribué des valeurs aux éléments de preuve après avoir étudié les données et atteint le consensus.
Avantages, préjudices et coûts : L'amélioration de l'efficacité et du respect des protocoles de courte durée devrait réduire le taux d'échec du traitement chez les enfants du Canada et le coût des soins antituberculeux.
Recommandations : On recommande un protocole de courte durée (6 mois) constitué de quatre médicaments au cours des deux premiers mois et de deux médicaments au cours des quatre mois suivants pour traiter la tuberculose pulmonaire ou une tuberculose extrapulmonaire cause de lymphadénopathie. La méningite tuberculeuse, la tuberculose qui atteint les os et les articulations, et la tuberculose doublée d'une infection à VIH, nécessitent des traitements de plus longue durée. Il faudrait traiter la tuberculose asymptomatique à l'aide de doses quotidiennes d'isoniazide pendant 9 mois. Un traitement intermittent sous observation directe est recommandé si l'on ne peut assurer le respect du traitement. On ne recommande pas des analyses routinières de la fonction hépatique chez les enfants prépubertaires qui prennent de l'isoniazide, mais on recommande une évaluation mensuelle des symptômes cliniques. Une évaluation périodique de la fonction hépatique est recommandée chez les adolescentes, particulièrement après un accouchement.
Validation : Ce rapport a été examiné par les directeurs de la Société canadienne de pédiatrie, par la Division de l'hépatite et des pathogènes spéciaux du Laboratoire de lutte contre la maladie et par la Société canadienne de thoracologie. Les recommandations ressemblent à celles qu'est en train de formuler l'American Academy of Pediatrics.
Commanditaire : Les recommandations ont été formulées et appuyées par le Comité des maladies infectieuses et d'immunisation de la Société canadienne de pédiatrie.

The approach to chemotherapy for tuberculosis has undergone major changes in the past decade, with the demonstration that treatment of pulmonary tuberculosis with multiple potent antibacterial drugs in adults allows the treatment time to be shortened substantially.[1] At least eight studies have clearly shown that short-course (6-month) therapy is also efficacious in children and may lead to better compliance than long-course therapy.[2-9] This article provides background on and recommendations for short-course multi-drug treatment of tuberculosis in children based on a review of the data and a consensus of expert opinion.

Findings

Unique features of pediatric tuberculosis

In children, unlike in adults, tuberculous disease usually develops as an immediate complication of infection, typically as closed caseous lesions with relatively small numbers of mycobacteria.[10] Children have a greater propensity for extrapulmonary complications such as miliary tuberculosis, tuberculous meningitis and osteomyelitis.[10] Antituberculous therapy must include drugs capable of penetrating all tissues to minimize these complications.

Children also differ from adults in their risk of resistance developing during therapy ("secondary resistance"). Since this risk is proportional to the mycobacterial load in tissues, it is less of a problem in children than in adults, who experience a greater load. However, secondary resistance can occur in children, and primary resistance is an important problem for children infected by adults with drug-resistant tuberculosis.[10]

Children tolerate larger doses of antituberculous drugs per kilogram of body weight than adults and have fewer side effects. For example, hepatitis associated with isoniazid therapy is much less common in children than in adults,[10] and fatal hepatitis in children is exceedingly rare.[11] A recent review of possible deaths from isoniazid-associated hepatitis in the United States showed only rare instances in people less than 20 years of age.[12] Those at increased risk appear to be young women, particularly postpubescent Hispanic and black women, especially post partum.[12-14] Thus, routine liver function testing is not recommended for prepubescent children taking isoniazid. For adolescent young women, particularly those post partum, monthly evaluation for symptoms and periodic liver enzyme evaluation seem prudent.

Rationale for short-course regimens

The rationale for short-course therapy is the same

for adults and children. The mycobacterial population is thought to consist of organisms in three physiologic states: metabolically active, rapidly growing bacilli in areas with neutral pH, more slowly metabolizing organisms with spurts of activity in hypoxic and acidic areas, and very suppressed organisms in highly acidic areas (e.g., inside macrophages).[15] As shown in Table 1 the main antituberculous drugs (isoniazid, rifampin, pyrazinamide and streptomycin) differ in their primary sites of action and activity. Other drugs such as ethambutol, ethionamide and para-aminosalicylic acid prevent replication of the organism but do not readily kill it. The effectiveness of short-course multi-drug regimens depends on choosing the proper drug combinations to achieve adequate tissue and body fluid levels to kill *Mycobacterium tuberculosis* in all sites.[1,10]

Pulmonary tuberculosis

The eight pediatric studies of 6-month multi-drug therapy for pulmonary tuberculosis, which involved more than 1000 children, showed a combined success rate of greater than 95%.[2-9] Although the drug regimens differed slightly, all contained at least three drugs in the first 2 months of treatment followed by two bactericidal drugs in the 4-month completion phase. In some regimens three drugs were given throughout. In studies comparing intermittent and daily therapy during the completion phase no differences were found.[3,6] Although the samples were small, these studies showed the success rates of twice- or thrice-weekly therapy for 6 months to be equivalent to those of daily therapy.

Extrapulmonary tuberculosis

Unfortunately, large controlled studies of short-course multi-drug therapy for extrapulmonary tuberculosis in children are not available. For tuberculous meningitis a recent small nonrandomized study showed that a 6-month multi-drug regimen with pyrazinamide (isoniazid, rifampin, streptomycin and pyrazinamide for the first 2 months, and isoniazid and rifampin for the subse-

Table 1: Activity, site, dosage and main side effects of main antituberculous drugs

Drug	Activity	Penetration of cavities	Dose, mg/kg (maximum dose, mg)*		Main side effects in children
			Daily	Twice weekly	
Isoniazid	Bactericidal, intracellular, extracellular	Excellent	10–15 (300)	20–40 (900)	Hepatic enzyme elevation, hepatitis, peripheral neuropathy, fever, rash
Rifampin	Bactericidal, intracellular, extracellular; active against slow-growing bacteria	Excellent	10–20 (600)	10–20 (600)	Orange discoloration of urine, secretions, nausea, hepatitis
Pyrazinamide	Bactericidal only at acidic pH (e.g., intracellular)	Excellent	20–40 (2000)	50–70 (2000)	Rare: hepatotoxicity, elevated uric acid level, arthralgia, rash, gastrointestinal upset
Streptomycin	Bactericidal, extracellular; excluded from intracellular environment	Adequate but poor penetration of cerebrospinal fluid	20–40 (1000)	20–40 (1000)	Ototoxicity, nephrotoxicity
Ethambutol	Bacteriostatic at low daily dose (15 mg/kg); bactericidal at higher daily dose (25 mg/kg)	Good	15–25 (2500)	50 (2500)	Optic neuritis† (decreased red, green colour discrimination; decreased visual acuity), rash

*All drugs to be taken orally except streptomycin, which is administered intramuscularly.
†Because of the difficulty in assessing visual acuity in young children, this drug is not recommended for this group.

quent 4 months) was more efficacious than 9- and 12-month multi-drug regimens that did not contain pyrazinamide.[16] Studies comparing 6- and 9-month multi-drug regimens that include pyrazinamide are not yet available.

Data supporting short-course multi-drug therapy for other forms of extrapulmonary tuberculosis in children are also sparse. Several of the 6-month trials of therapy for pulmonary tuberculosis in children showed favourable outcomes in a few cases of adenitis and disseminated tuberculosis, which indicates that short-course multi-drug therapy may be appropriate for extrapulmonary as well as pulmonary disease.[5,6] A large trial of short-course therapy for extrapulmonary disease involving 332 adults and 18 children 15 years of age or less showed a success rate of greater than 95% and thus supports this recommendation.[16] However, tuberculosis involving the bones and joints, and possibly miliary or disseminated tuberculosis, may not be as amenable to short courses of treatment. A 6-month study of multi-drug therapy for tuberculous bone and joint disease had an unacceptably high failure rate of 23%.[16] Extended courses of 9 to 12 months appear to be more prudent, and surgical débridement may be a helpful component.

There is concern that short-course therapy for miliary or disseminated disease is inappropriate because of the high bacillary load associated with these conditions. Because large trials of such therapy are not available and tuberculous meningitis can also have a moderately large bacillary load some experts suggest that the more intensive protocol (2 months of treatment with four drugs including pyrazinamide followed by at least 4 to 6 months of treatment with isoniazid and rifampin) is safer than the short-course protocol.[10]

If used in the early stages of tuberculous meningitis adjunctive therapy with drugs such as corticosteroids has been shown to decrease rates of death and long-term neurologic sequelae.[17,18] The role of corticosteroids in treating other forms of tuberculosis in children is less clear, but they may be beneficial in children with enlarged hilar lymph nodes that compromise the tracheobronchial tree,[19] in miliary disease with alveolar-capillary block, pleural effusions and pericardial effusions and in obstructive endobronchial disease.[10]

The optimal length of multi-drug therapy in immunocompromised children such as those with HIV infection is unknown. Currently, adults with HIV infection and tuberculosis receive multi-drug therapy for 9 months or for 6 months after the last positive sputum culture result, whichever is longer.[20] Initial therapy with four drugs is recommended for these adults. For children with HIV infection who are suspected of having tuberculosis some experts suggest an extended course of therapy similar to that recommended for tuberculous bone and joint disease (e.g., isoniazid, rifampin and pyrazinamide for 2 months followed by isoniazid and rifampin for 7 to 10 months).[10] Since the degree of immunodeficiency in such children varies, discussion with an expert concerning selection of drugs and length of therapy is recommended.

Drug-resistant tuberculosis

Drug resistance in children occurs more often from the transmission of a resistant strain from an adult than from the development of resistant bacteria during treatment. Drug resistance is a major concern if the patient does not respond to initial therapy or has a relapse. Fortunately, in Canada single-drug resistance is still uncommon and multi-drug resistance rare (Donna L. Holton, MD, chief of Hepatitis and Special Pathogens Division, Laboratory Centre for Disease Control, Ottawa: personal communication, 1994). However, in the United States multi-drug-resistant tuberculosis is an increasing problem in certain regions and groups.[21] An increase in the prevalence of tuberculosis, delays in diagnosis, inappropriate treatment protocols, poor compliance and disease in patients with HIV infection have contributed to multi-drug resistance. The probability of resistance can be minimized with early diagnosis and appropriate treatment regimens that ensure compliance.

For drug-resistant tuberculosis, protocols must include at least two bactericidal drugs to which the isolate is susceptible and an extended length of treatment, especially in immunocompromised patients.[1,10] Particular care must be taken in selecting the drug combinations. For example, although primary resistance to pyrazinamide is rare, the drug may not be effective in preventing rifampin resistance during therapy if the bacteria are already resistant to isoniazid.[10] Given the complexity of selecting antimicrobial drugs and determining the length of therapy, discussion with an expert is recommended if drug-resistant tuberculosis is suspected or diagnosed.

Asymptomatic tuberculosis

The best-studied regimen for preventive therapy for asymptomatic tuberculosis is 10 mg/kg per day of isoniazid, not to exceed 300 mg per day, in a single oral dose for 12 months. This regimen is almost 100% effective in children and protects them for at least 30 years.[22] The optimal duration of preventive therapy with isoniazid is still controversial. The results of a large placebo-controlled trial involving adults suggested that the duration of prophylaxis can be shortened to 6 months if there is good compliance.[23] Since there are no comparable data on short-course preventive regimens in children and since the risk of disease and dissemination is higher in children than in adults,[10] most authorities recommend at least 9 months of preventive therapy in children.[10] However, longer courses are indicated in immunocompromised children. Large studies of preventive therapy for isoniazid-resistant tuberculosis or in patients unable to take isoniazid are not available; however, some experts recommend 15 mg/kg per day of rifampin for 9

months.[10] Trials of preventive treatment of multi-drug-resistant tuberculosis have not been conducted. Drug combinations such as ethambutol and pyrazinamide or pyrazinamide and rifampin for 5 to 12 months have been suggested.[24]

Compliance

An advantage of short-course multi-drug therapy for susceptible tuberculosis is improved compliance. Biddulph[5] has shown that drug selection for short-course therapy can significantly affect compliance. More children dropped out of a study arm that included streptomycin administered intramuscularly than one of isoniazid, rifampin and pyrazinamide given orally, which indicated that regular injections deterred compliance. Directly supervised therapy twice or thrice weekly can further improve compliance and is less expensive in a short course than in a long course. For adults, studies showed that directly observed therapy made a clear difference in efficacy because of improved compliance.[25–27] Thus, if patients are unlikely to be compliant, directly observed therapy is recommended.

Follow-up of children with tuberculosis

Follow-up of patients with tuberculosis is crucial to verify compliance, monitor clinical response and detect any adverse reactions to medications.[10] In general, patients should be seen monthly and given only enough medication to last until the next visit. The rates of adverse reactions to antituberculous medications among prepubescent children are low enough that routine biochemical monitoring is unnecessary. If the child or family report persistent anorexia, vomiting or abdominal pain, or if jaundice is evident, the patient should be told to stop taking all medications until a complete examination and blood tests are performed.[10] Low-level increases in serum liver enzymes (i.e., to two to four times the normal level) do not necessitate cessation of treatment if

Table 2: Recommended protocols for treatment of tuberculosis in infants, children and adolescents

Form of tuberculosis	Length of therapy, mo	Drug regimen	Remarks
Asymptomatic (positive Mantoux test result, no clinical or radiologic changes of disease)	9	Isoniazid daily	If compliance is a problem choose twice-weekly supervised therapy. If isoniazid-resistant strain consider rifampin. If multi-drug-resistant strain consult local expert
Pulmonary	6	Isoniazid, rifampin and pyrazinamide daily for 2 mo, then isoniazid and rifampin daily or twice weekly for 4 mo	If compliance is a problem choose twice-weekly supervised therapy. If drug-resistant strain adjust regimen to include at least two bactericidal drugs to which the organism is sensitive, extend length of therapy if necessary
Extrapulmonary			
Meningitis, disseminated (miliary) or congenital infection	6–9	Isoniazid, rifampin pyrazinamide and streptomycin* daily for 2 mo, then isoniazid and rifampin daily for 4–7 mo	Corticosteroids (e.g., prednisone, 1–2 mg/kg daily for 4–6 wk) are beneficial in the early stages of tuberculous meningitis
Bone and joint disease	9–12	Isoniazid, rifampin and pyrazinamide daily for 2 mo, then isoniazid and rifampin daily for 7–10 mo	
Other extrapulmonary e.g., lymphadenopathy	6	Isoniazid, rifampin and pyrazinamide daily for 2 mo, then isoniazid and rifampin daily or twice weekly for 4 mo	
Any form in immunocompromised patient (e.g., with HIV infection)	9–12	Isoniazid, rifampin and pyrazinamide daily for 2 mo, then isoniazid and rifampin daily for 7–10 mo	Diagnosis may be difficult; discuss with a local expert

*If streptomycin is not readily available consult the local health unit.

all other findings are normal. Since adolescents, especially women, are at higher risk for isoniazid-associated hepatitis, monthly evalution for symptoms and periodic liver enzyme evaluation is recommended. If ethambutol is used visual acuity and colour discrimination in each eye should be checked before therapy starts and monthly during therapy. Ethambutol is not recommended for routine use in young children because of the difficulty in assessing visual acuity in children. However, if used, regular ophthalmologic assessment must be done. If streptomycin is used a screening hearing test should be performed monthly to monitor the drug's potential ototoxic effects.

Since pulmonary tuberculosis recedes slowly in children frequent chest radiographs are not indicated. It is usually sufficient to obtain chest radiographs at diagnosis, after 1 or 2 months of therapy (to ensure that no unusual changes have occurred) and upon completion of therapy. Since hilar lymphadenopathy may take several years to resolve,[8] persistence of this symptom after the 6-month multi-drug regimen does not indicate a need to continue therapy. After therapy children should be seen at 3- to 6-month intervals to follow improvement shown by radiographs.

Noncompliance with drug therapy is a major problem in tuberculosis control, and potential noncompliance should be assessed at the start of therapy. If it is expected a twice-weekly multi-drug short-course regimen directly supervised by a health care professional should be chosen. This type of program may be arranged in collaboration with the local health unit. Twice-weekly unsupervised therapy is not recommended for children.

All cases of tuberculosis must be reported to the local public health authorities[28] to ensure tracing and treatment of contacts and to help prevent the spread of the bacteria by detecting the adult sources of the pediatric infection. Detection of the adult sources may also facilitate isolation of the organism for sensitivity testing.

Recommendations

On the basis of these findings we strongly recommend short-course multi-drug therapy for infants, children and adolescents with tuberculosis.

These intensive short-course multi-drug protocols have been shown to be effective and are well tolerated by children. Early aggressive therapy with good compliance can diminish the prevalence of serious tuberculosis and minimize the emergence of resistant organisms. Intermittent short-course therapy should be considered for children if direct supervision is required to ensure compliance. Such supervised protocols are less costly than the previously recommended longer regimens. Unsupervised intermittent therapy is not recommended.

Specific drug dosages and precautions are given in Table 1, and treatment regimens for different forms of tuberculosis in infants, children and adolescents are presented in Table 2. Routine liver function testing is not recommended for prepubescent children taking isoniazid but is recommended for adolescent women, especially post partum. In children treated with isoniazid peripheral neuritis and convulsions caused by inhibition of pyridoxine metabolism are very rare. Thus, such children do not need pyridoxine supplements unless they have a nutritional deficiency, are on a strict vegetarian diet or are being breast-fed. If isoniazid-resistant tuberculosis is suspected or proven, regimens must be modified as noted in Table 2. If multi-drug resistance is a concern, consultation with a local expert is recommended to tailor therapy to overcome the resistance.

Validation

These recommendations were reviewed by the directors of the Canadian Paediatric Society, the Hepatitis and Special Pathogens Division of the Laboratory Centre for Disease Control and the Canadian Thoracic Society. They are similar to recommendations of the American Academy of Pediatrics.[29]

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Conferences
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May 1–5, 1994: 20th Canadian Medical and Biological Engineering Conference
Vancouver
CMBEC Secretariat, c/o National Research Council of Canada, Rm. 393, Building M-55, Ottawa, ON K1A 0R8; tel (613) 993-1686, fax (613) 954-2216

Du 1er au 5 mai 1994 : 20e Conférence canadienne de génie biomédical
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May 4, 1994: Health Care in Canada: Taming the Cost Lion (sponsored by Financial Post Conferences and Ernst and Young)
Toronto
Financial Post Conferences, 333 King St. E, 3rd floor, Toronto, ON M5A 4N2; tel (416) 350-6207, fax (416) 350-6201

May 5–6, 1994: Ontario Gerontology Association 13th Annual Conference: the Challenge of Change
Toronto
Speaker: Fay Lomax Cook
Ontario Gerontology Association, 7777 Keele St., 2nd floor, Concord, ON L4K 1Y7; tel (905) 660-1056, fax (905) 660-7450

May 6, 1994: 19th Annual Medical Clinic Day — Heart and Soul
North York, Ont.
Sybil Gilinsky, Education Department, Baycrest Centre for Geriatric Care, 3560 Bathurst St., North York, ON M6A 2E1; tel (416) 789-5131, ext. 2365

May 6–7, 1994: Quebec Scoliosis Society 24th Annual Meeting
Quebec City
Dr. Benoit Morin, secretary, Quebec Scoliosis Society; tel (514) 345-4876, fax (514) 345-4755

Les 6 et 7 mai 1994 : Société de la scoliose du Québec 24e réunion annuelle
Québec
Dr Benoit Morin, secrétaire, Société de la scoliose du Québec; tél (514) 345-4876, fax (514) 345-4755

May 6–8, 1994: Queensland Branch of the Australian Medical Association Centenary Weekend
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